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Recollections of Whittingehame Lodge

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I first met Fisher at the Stockholm International Congress of Genetics (1948). I introduced myself—I was at the time a microbial geneticist, one of the very few (five or six, perhaps) in existence— and after five minutes of conversation, he offered me a job at Cambridge in his department for setting up a laboratory to work on crossing over in bacteria. Joshua Lederberg had just published (1947) the details of his discovery of recombination in *E. coli*, and Fisher was interested in the theory of crossing over. He hoped bacteria would provide excellent data to test his theory, which was further developed and later published mostly by A. R. G. Owen.

I was utterly surprised that he would offer on the spot a position to a very young and unknown person from a country which had, especially at the time, a rather poor reputation in England. But I was, of course, delighted, and accepted. He might have learned about me in advance from Kenneth Mather, one of his favorite disciples. I was at the time working with Mather at the John Innes Horticultural Institution on linkage of quantitative traits in Drosophila, and he might have told Fisher about me. He later advised me on relations with Fisher, telling me that the first fifteen days would have decided whether he would have liked and accepted me among his friends or me put in the opposite category. Fisher was certainly a man of strong likes and dislikes; he was extremely generous and charming to his friends (all of whom adored him) and hard on people he did not like. Karl Pearson was certainly at the top of his blacklist, as Fisher knew that Pearson had tried to crush his scientific career at its beginning, and never forgave him for that. I was very lucky to be one of those he liked, and he was extremely generous with me. I had a chance to have many long conversations with him at Caius College and he frequently invited all my family to have lunch in good restaurants. He was not at all disgruntled when I left him after two years (earlier than expected), having found what seemed a good position in Italy, and he continued to be very friendly. Above all, I owe him an enormous scientific debt.

At the time, the Cambridge Genetics Department was located at Whittingehame Lodge, at 44 Storey's Way, somewhat far from the center

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of town. The Lodge was really meant to be his house, and it came with the chair. But the University refused to give him adequate space for his laboratory, and Fisher decided to use the Lodge for this purpose, keeping one bedroom for himself or visitors, and sleeping and eating most of the time at Caius College, where he was a Fellow. The large garden was used by him for his plant breeding experiments, and the house was turned into a mouse laboratory. I was given half of the room where people of the Department used to have tea, and built in it my bacteriological laboratory. I had also a little office with an excellent Friden calculator, like everybody else in the Department. Mr. Harry Moule, a long-time technical assistant of Fisher who had in his early days worked in a bacteriological laboratory, helped me part-time with my cultures. I was also asked to give a course in Microbial Genetics, probably the first ever; and Fisher bicycled to all my lectures. This was his usual way of going to town. Lectures were arranged so that they would end by the time pubs would open; and afterwards we spent an hour or so at the nearest one, sipping beer and discussing the lecture.

In that period, and for all of the years he was at Cambridge, Fisher's time was divided between mice or plant breeding, and work at his desk calculator. Mouse research was almost entirely dedicated to linkage studies, and he spent several hours every day scoring his mice. As is well known, Fisher was extremely nearsighted. In spite of his bad sight, or because of it, he could do one job which is very difficult if not impossible for the visually-normal breeder: score the sex of newborn mice. He used to take the little creatures and, without glasses, bring them to a distance of one inch from one of his eyes. His nearsightedness allowed him a sharp vision under these conditions with, I believe, an adequate magnification. It was Fisher's enthusiasm for linkage that prompted him to ask me to set up a laboratory of microbial genetics. He understood immediately the procedure for calculating recombination frequencies used (and not specified) by Lederberg in his 1947 paper. The procedure was made necessary by the fact that non-recombinants had to be eliminated and only certain classes of recombinants allowed to grow in the selective media necessary for studying bacterial recombination. These constraints, and further developments which proved quite interesting but showed the presence of unforeseen complications, made it eventually impossible to satisfy his initial desire, that of using bacteria as the ideal organisms for the study of the formal theory of recombination.

Fisher also cultivated all Mendel's varieties of peas in the garden of the department as a tribute to Mendel. It is certainly not true that Fisher kept making disparaging remarks on Mendel for having willingly fudged his data. Although Fisher discovered that Mendel's chi squares were too good for the data to be true, Beadle was unjust in attacking Fisher on this point

at the 1965 centennial meeting of Mendel's laws, held in Colorado. I heard Fisher say at a lecture of his regular course (in 1949) that he did not believe Mendel had consciously fudged the data. He conjectured that the abbot had a clever gardener who helped him with his breeding work, and who understood or knew exactly what Mendel expected. Fisher thought that the abbot was easily upset when the segregations did not look right, and that the gardener avoided that unpleasant development by suppressing some of the plants that caused a deviation from the expected proportions.

In the period I worked in Fisher's department (1948–1950), a meeting on human genetics was organized in Milan, Italy, by Adriano Buzzati-Traverso, who was my first teacher of genetics. Both Fisher and Haldane were invited among other guests, but, as most English geneticists knew, they did not like each other too much. It looked as if England was too small a country for the two geniuses, both of approximately the same age and both interested in very similar problems. At the meetings of the Genetical Society of Great Britain, which took place three or four times a year, the presence of both inevitably generated very lively discussions. The same happened in Milan. The meeting turned out to be a historic one, and it is unfortunate that to my knowledge all copies of the printed proceedings have disappeared, including mine. Fisher spoke about the importance of genetic linkage in humans and the necessity of producing linkage maps, among other reasons for applications to genetic diseases of which he mentioned, for instance, Huntington's chorea. Fisher's prophecy came true only in the eighties, and genetic linkage is now the most active field in human genetics. At the time, there were too few markers known and no real examples that he could cite, except a couple of possible partial sex linkages. These had been suggested by Haldane—incidentally, they were later shown to be invalid. In the discussion, Haldane remarked sourly that the example cited by Fisher was first produced by him.

In his paper at the Milan meeting, Haldane made for the first time the suggestion that diseases like thalassemia (very common in some Italian regions) and sickle cell anemia could reach high frequencies because of selective advantage of the heterozygotes in malarial regions, where the diseases afflicting the homozygotes were known to be frequent. This suggestion was later proved to be correct in Africa for sickle cell anemia by Allison, and is believed to hold also in other cases including thalassemia and G6PD (glucose-6-phosphate dehydrogenase). In the discussion, Fisher reminded Haldane that he had first shown that gene frequencies reach a stable intermediate equilibrium when the heterozygote has a selective advantage over both homozygotes (1922), four years before Haldane published a similar paper.

Many papers of his friends really originated from Fisher's ideas. I wanted to test if observed curves of selection for heterozygotes in artificial popula-

tions of *Drosophila* had the expected shape and asked advice of him. The next morning he gave me a sheet of paper with one formula, without adding any further word. It took me some time to discover that it was the solution of the differential equation of the process of selection for the heterozygote. The formula was quite useful because it could be used to linearize the gene frequencies with time. When I was looking for a genetic distance to build my evolutionary trees, I asked his advice again and he suggested a generalization of the cosine transformation of percentages to include multiple alleles, which I later adapted to my problem. The same generalization was published by Bhattacharyya; I do not know if this was known to Fisher, but he did not mention it to me, and I discovered Bhattacharyya's contribution much later, so that I attributed the formula to Fisher in my early papers.

More important ideas I owe to Fisher's work include the logarithmic distribution, which I could show can be obtained for large N from Karlin and MacGregor's distribution of mutant forms in populations. We used Fisher's formula, originally developed for the ecological problem of species abundance, for fitting surnames distributions (Zei *et al.*, 1983). It is easier to fit than Karlin and MacGregor's and gives almost indistinguishable results.

The most rewarding application I made of Fisher's ideas was based on his "theory of the wave of advance of advantageous genes." I learned about it by perusing reprints of his work when I was at Cambridge. Later Skellam showed that the same theory can be applied to the spread of a population, and I found it very handy when I was interested in describing the diffusion of neolithic farmers to Europe, starting from the mid-eastern Fertile Crescent (Ammerman and Cavalli-Sforza 1972, 1984). When I had the honor of being invited to give the Sixth Memorial Fisher Lecture in London (24 June 1974), I thought this was the most appropriate subject.

But another very important legacy I received from Fisher was the chance to establish important bonds between some of his students and myself. I owe it to the collaboration with Anthony Edwards if we were able to develop the first phylogenetic trees of the human species (Cavalli-Sforza and Edwards, 1964; Edwards and Cavalli-Sforza, 1964), and to that with Walter Bodmer, a ponderous volume on "The Genetics of Human Populations" (1971) which greatly increased my understanding of the subject, and perhaps Bodmer's as well. Much of my scientific future was forged in those two eventful years in which I worked at Whittingehame Lodge.

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